

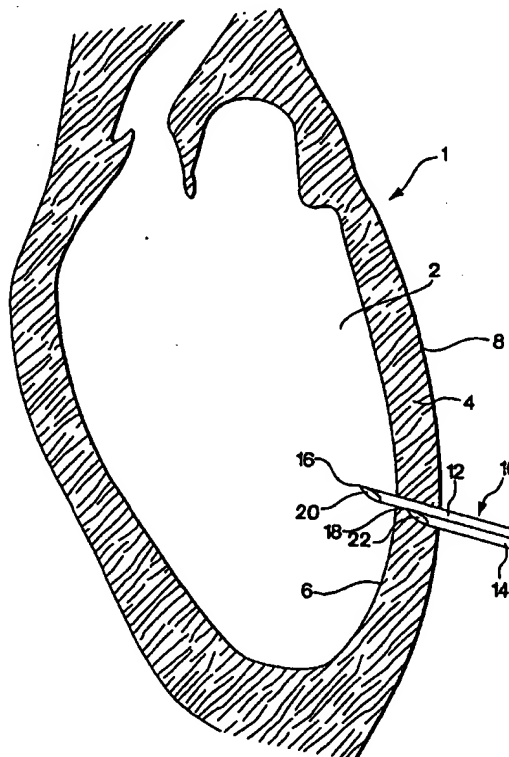
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(21) International Application Number: PCT/US99/22541 (22) International Filing Date: 30 September 1999 (30.09.99) (30) Priority Data: 09/164,164 30 September 1998 (30.09.98) US (71) Applicant: C.R. BARD, INC. [US/US]; 730 Central Avenue, Murray Hill, NJ 07974 (US). (72) Inventors: GAMBALE, Richard, A.; 382 Dunstable Road, Tyngsboro, MA 01879 (US). FORCUCCI, Stephen, J.; 84 Hibbert Street, Arlington, MA 02174 (US). CHOH, Richard, T.; P.O. Box 1332, Waltham, MA 02154 (US). CAFFERATA, Robert; 55 Warwick Road, Belmont, MA 02478 (US). (74) Agent: PERULLO, John, F.; Kirkpatrick & Lockhart LLP, 75 State Street, Boston, MA 02109-1808 (US).		(81) Designated States: CA, JP, MX, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>Without international search report and to be republished upon receipt of that report.</i>

(54) Title: TRANSTHORACIC DRUG DELIVERY DEVICE**(57) Abstract**

The present invention provides a transthoracic drug delivery device (10) that utilizes pressure to determine the precise location of the distal tip (18) of the delivery tube (14) of the device to insure that therapeutic substances are ejected into the myocardium (4) and not dissipated in unintended tissue locations. In one embodiment the drug delivery device (10) comprises a pressure sensing tube (12) mounted in parallel to a drug delivery tube (14) wherein the tubes are staggered so that the pressure tube (12) extends beyond the delivery tube (14). In another embodiment, a steerable syringe is provided so that multiple sites in the myocardium can be treated with a therapeutic substance with only one penetration into the heart. Once the delivery tube (28) of the syringe penetrates the left ventricle, its distal tip (32) can be deflected back toward the endocardial surface (6) and the tube (28) withdrawn proximally to cause penetration of the tip (32) into the myocardium (4). The deflectable tip (32) can be adjusted to a different deflection angle and the delivery tube (28) rotated to make available a circular array of points that may be accessed by the syringe.



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TRANSTHORACIC DRUG DELIVERY DEVICE

Field of the Invention

The present invention relates to a device and method for delivering a
5 therapeutic substance to the myocardium of a human heart.

Background of the Invention

Tissue becomes ischemic when it is deprived of adequate blood flow. Ischemia causes pain in the area of the affected tissue and, in the case of muscle
10 tissue, can interrupt muscular function. Left untreated, ischemic tissue can become infarcted and permanently non-functioning. Ischemia can be caused by a blockage in the vascular system that prohibits oxygenated blood from reaching the affected tissue area. However, ischemic tissue can be revived to function normally despite the deprivation of oxygenated blood because ischemic tissue can remain in a hibernating
15 state, preserving its viability for some time. Restoring blood flow to the ischemic region serves to revive the ischemic tissue.

Although ischemia can occur in various regions of the body, often tissue of the heart, the myocardium, is affected by ischemia due to coronary artery disease, occlusion of the coronary arteries, which otherwise provides blood to the myocardium. Muscle
20 tissue affected by ischemia can cause pain and lead to infarction of the tissue. Ischemia can be treated, if a tissue has remained viable despite the deprivation of oxygenated blood, by restoring blood flow to the affected tissue.

Treatment of myocardial ischemia has been addressed by several techniques designed to restore blood supply to the affected region. Coronary artery bypass
25 grafting CABG involves grafting a venous segment between the aorta and the coronary artery to bypass the occluded portion of the artery. Once blood flow is redirected to the portion of the coronary artery beyond the occlusion, the supply of oxygenated blood is restored to the area of ischemic tissue.

Early researchers, more than thirty years ago, reported promising results for

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revascularizing the myocardium by piercing the muscle to create multiple channels for blood flow. Sen, P.K. et al., "Transmyocardial Acupuncture - A New Approach to Myocardial Revascularization", *Journal of Thoracic and Cardiovascular Surgery*, Vol. 50, No. 2, August 1965, pp. 181-189. Although others have reported varying degrees of success with various methods of piercing the myocardium to restore blood flow to the muscle, many have faced common problems such as closure of the created channels. Various techniques of perforating the muscle tissue to avoid closure have been reported by researchers. These techniques include piercing with a solid sharp tip wire, hypodermic tube and physically stretching the channel after its formation. Reportedly, many of these methods still produced trauma and tearing of the tissue that ultimately led to closure of the channel.

An alternative method of creating channels that potentially avoids the problem of closure involves the use of laser technology. Researchers have reported success in maintaining patent channels in the myocardium by forming the channels with the heat energy of a laser. Mirhoseini, M. et al., "Revascularization of the Heart by Laser", *Journal of Microsurgery*, Vol. 2, No. 4, June 1981, pp. 253-260. The laser was said to form channels in the tissue that were clean and made without tearing and trauma, suggesting that scarring does not occur and the channels are less likely to experience the closure that results from healing. U.S. Patent No. 5,769,843 (Abela et al.) discloses creating laser-made TMR channels utilizing a catheter based system. Abela also discloses a magnetic navigation system to guide the catheter to the desired position within the heart. Aita patents 5,380,316 and 5,389,096 disclose another approach to a catheter based system for TMR.

Although there has been some published recognition of the desirability of performing transmyocardial revascularization (TMR) in a non-laser catheterization procedure, there does not appear to be evidence that such procedures have been put into practice. For example, U.S. Patent No. 5,429,144 Wilk discloses inserting an expandable implant within a preformed channel created within the myocardium for the purposes of creating blood flow into the tissue from the left ventricle.

Performing TMR by placing stents in the myocardium is also disclosed in U.S.

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Patent No. 5,810,836 (Hussein et al.). The Hussein patent discloses several stent embodiments that are delivered through the epicardium of the heart, into the myocardium and positioned to be open to the left ventricle. The stents are intended to maintain an open channel in the myocardium through which blood enters from the ventricle and perfuses into the myocardium.

Angiogenesis, the growth of new blood vessels in tissue, has been the subject of increased study in recent years. Such blood vessel growth provides new supplies of oxygenated blood to a region of tissue that has the potential to remedy a variety of tissue and muscular ailments, particularly ischemia. Primarily, the study has focused on perfecting angiogenic factors such as human growth factors produced from genetic engineering techniques. It has been reported that injection of such a growth factor into myocardial tissue initiates angiogenesis at that site, which is exhibited by a new dense capillary network within the tissue. Schumacher et al., "Induction of Neo-Angiogenesis in Ischemic Myocardium by Human Growth Factors", *Circulation*, 1998; 97:645-650. The authors noted that such treatment could be an approach to management of diffused coronary heart disease after alternative methods of administration have been developed.

Mechanical devices have been disclosed for delivering therapeutic substances to the myocardium. International patent publication no. WO 98/05307 by Local Med, Inc. discloses a method of using a conventional, rigid syringe to access the myocardium and left ventricle to deliver a therapeutic substance such as an angiogenic factor.

Summary of the Invention

The present invention provides a transthoracic drug delivery device that is specially configured to be precisely located in the myocardium for accurate placement of a therapeutic substance such as a drug. The device comprises a syringe having a delivery that is capable of penetrating the myocardium via the epicardium to access the left ventricle. Access to the heart is gained through the thorax. A pressure monitor associated with the device indicates the position of the distal tip of the

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delivery tube. It is noted that, throughout the discussion of the invention in the specification, "distal" is meant to indicate the direction along the access path of the device leading internal to the patient and "proximal" indicates the direction along the access path leading external to the patient. Pressure may be monitored through the delivery tube or through a separate pressure tube associated with the delivery tube. Specifically, the amount of pressure measured through the tube of the device informs the physician whether the distal port of the tube has penetrated the myocardium completely to reach the left ventricle. In the case of separate delivery and pressure tubes, the distance between the pressure tube opening and drug delivery tube opening is known, so the user can determine whether the drug delivery tube opening is still within the myocardium, and, therefore, appropriately placed to inject a drug into the myocardium. Multiple drug delivery tubes may be associated with the device to perfuse the drug more quickly through multiple ports into the myocardium. It is noted that throughout the specification "drug" includes all varieties of therapeutic substances that may be beneficial to the body, including pharmaceutical agents, genetically engineered substances or natural substances.

In another embodiment, a pressure sensing hypodermic tube, as in the first embodiment, is used to transthoracically access the heart and penetrate the left ventricle. However, the second embodiment is comprised of a single pressure sensing tube. The distal portion of the pressure tube is flexible and made controllable or steerable by mechanisms well known in the art of catheter manufacture such as a pull wire bonded to the distal end of the tube and extending proximally for manipulation outside the patient. After penetrating the left ventricle, the single pressure tube may be bent into a "J" configuration and the shaft withdrawn proximally to cause the curved tip of the J portion to penetrate the myocardium again, through the endocardial surface while moving in a proximal direction, similar to a fish hook. Entrance of the distal port of the pressure tube into the tissue results in a drop of measured pressure, indicating to the user that the distal tip of the pressure tube is within tissue, and, thus, appropriately placed to inject the drug or therapeutic substance being carried by the device.

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After delivery of the therapeutic substance to a first location, the distal tip of the pressure tube may be backed out of the tissue by distal movement of the device into the ventricle and another location accessed. The steerable distal tip of the device permits the distal tip to be deflected through various angles relative to the longitudinal axis of the tube. Combining this range of movement with the rotational capability inherent in the device provides a locus of points about the penetration point into the ventricle where the distal tip of the needle can be placed into the myocardium to deliver therapeutic substances.

It is an object of the present invention to provide a drug delivery device that can access the myocardium and left ventricle of the heart transthoracically and accurately indicate the position of the distal tip of the device within the heart.

It is another object of the invention to provide a drug delivery device that is capable of delivering a therapeutic substance to the myocardium of the heart accurately and easily.

It is yet another object of the invention to provide a drug delivery device that is capable of delivering a therapeutic substance to the myocardium of the heart quickly via a plurality of delivery conduits.

It is yet another object of the invention to provide a drug delivery device that is capable of reaching a plurality of delivery locations in the myocardium with a single access to the heart.

It is yet another object of the invention to provide a drug delivery device for placement within the heart that is associated with a pressure sensor having adequate sensitivity to discern whether the pressure sensor port is within the myocardium or within the left ventricle.

It is yet another object of the invention to provide a delivery device that is configured to have a deflectable tip so that the reverse side of tissue having been accessed by the device can also be penetrated by the sharp tip of the device as the device is moved back along its access path.

Brief Description of the Drawings

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The foregoing and other objects and advantages of the invention will be appreciated more fully from the following further description thereof, with reference to the accompanying diagrammatic drawings wherein:

FIG. 1 is a diagrammatic, sectional illustration of the left ventricle of the human heart having the drug delivery device of the present invention inserted through the myocardial tissue;

FIG. 2 is a detailed sectional illustration of a portion of myocardial tissue that has been penetrated by the drug delivery device of the present invention;

FIG. 3 is a detailed sectional illustration of a portion of myocardial tissue that has been penetrated by an alternate embodiment of the drug delivery device of the present invention;

FIG. 4 is a diagrammatic, sectional illustration of the left ventricle of the human heart wherein the myocardium has been penetrated by a second embodiment of the drug delivery device; and

FIGS. 5-8 show a series of detailed sectional illustrations of a portion of the myocardium having been penetrated by the second embodiment of the delivery device.

Description of the Illustrative Embodiment

20

FIG. 1 shows a sectional view of the left ventricle of the heart having been penetrated by the drug delivery device of the present invention. The multiple tube embodiment 10 is comprised of a pressure tube 12 for monitoring pressure and a delivery tube 14 for dispensing the therapeutic substance or drug into the myocardium

4. The tubes may comprise metal hypodermic tubing or any tubing capable of being configured to have sufficient strength and sharpness to penetrate tissue. The tubes are joined together side-by-side in parallel relationship, but are offset so that the pressure tube extends beyond the delivery tube. Both the pressure tube 12 and delivery tube 14 have sharpened distal tips 16 and 18 and open distal ports 20 and 22, respectively. The device is delivered through the thorax and epicardial surface 8

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of the heart and advanced through the myocardium 4 until the pressure tube 12 penetrates the left ventricle 2. Alternatively, as will be described in further detail below, the tubes may be formed from relatively flexible material having rigid sharp inserts at the distal ends and the flexible tubes being temporarily fortified to resist buckling during delivery by an inner stiffening element that may be withdrawn after delivery.

The proximal end of the delivery tube 14 is joined to a pressurized source of a therapeutic substance such as may be provided by a syringe (not shown). The pressure tube is joined at its proximal end 24 to a pressure monitor (not shown) for measuring the pressure sensed at the pressure tube distal port 20. As the pressure tube is inserted through the tissue of the heart, measured pressure will be low; however, once the pressure port 20 reaches the left ventricle 2, measured pressure increases dramatically signaling the physician that the ventricle has been reached.

The distance D between the relative longitudinal spacing of the pressure tube and delivery tube (measured from distal tip 16 to distal tip 18) is known. Therefore, at the moment during advancement of the device into the heart when pressure dramatically increases, not only is the position of distal tip 16 known (having penetrated the endocardial surface 6 to access the ventricle 2) but also, the position of the delivery tube distal tip 18 will be known relative to the endocardial surface 6. Therefore, if it is desired to deliver a therapeutic substance to a certain depth beneath the endocardial surface 6 of the myocardium 4, the pressure and delivery tubes 12 and 16 can be arranged relative to each other to provide that distance D between their distal tips 16 and 18. Upon penetration of the ventricle, the therapeutic substance can be discharged from the delivery port 22 at the desired distance beneath the endocardial surface 6. During this procedure, the pressure tube 12 may also be used to inject contrast media into the ventricle to help visualize the position of the device. FIG. 3 shows a variation of the multiple tube embodiment employing a plurality of delivery tubes, each spaced a distance beneath the distal tip of the pressure tube 12. The purpose of multiple delivery tubes is to provide increased drug

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delivery capability to surrounding myocardial tissue 4 with each penetration of the device into the heart.

The second embodiment of the drug delivery device further addresses the desirability of minimizing the number of times that the device must be inserted into the heart. A deflectable syringe tube 28 is shown in FIG. 4 protruding through the myocardium 4 into the left ventricle 2 of a human heart 1. After penetrating the myocardium, the distal portion 30 of the tube 28 may be deflected away from the longitudinal axis of the tube by as much as approximately 180°. The objective of providing such a large deflection is to permit the distal tip 32 of the tube to penetrate the endocardial surface 6 as the tube is withdrawn in a proximal direction from the ventricle 2. In the deflected configuration, the distal portion 30 of the tube is J-shaped and, therefore, pierces the tissue in similar fashion to a fishhook as it is withdrawn proximally. Once the distal port 34 has penetrated the myocardium, the therapeutic substance can be ejected through the port and into the tissue. The primary benefit provided by the deflectable tip tube is that multiple tissue locations can be reached with a single insertion penetration of the device into the heart.

As shown in FIG. 5, the tube should be inserted into the myocardium 4 while in a straight configuration. However, to be deflectable, at least the distal portion 30 of the tube must be flexible. Therefore, to provide sufficient longitudinal support during delivery through the heart tissue, a stiffening element 36 such as a stainless steel wire, may be advanced through the lumen 38 of the tube, extending to the distal tip 32. At least the proximal portion 30 of the tube should be fabricated from a relatively flexible material, such as a relatively low density polymer, to provide adequate flexibility for bending when the tip is deflected. The distal tip 32 may comprise an insert of a more rigid material bonded to the flexible material, such as a high density polymer or stainless steel to provide a sharp, piercing profile.

As shown in FIG. 6, after penetrating the myocardium 4, the stiffening element 36 is withdrawn proximally somewhat from the distal portion 30 of the tube 28 so that the tip 32 may be deflected to present its piercing distal tip 32 toward the endocardial surface 6 of the myocardium 4. The stiffening element 36 may, but need not be

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withdrawn completely from the tube to deflect the tip. The tip deflection may be actuated by a pull wire extending through the tube 28 and joined to the area of the distal tip 32. The pull wire extends proximally, out of the device so that it may be manipulated by the physician external to the patient. Pulling the pull wire puts tension
5 on one side of the tube which tends to cause the flexible distal portion 30 to curve in the direction that the tension is being applied. Such pull wire arrangements are well known in the catheter art and are not discussed in detail here.

As shown in FIG. 7, the deflected tip is drawn proximally into the endocardial surface 6. In this configuration, the therapeutic substance is ejected from the port 34
10 into the tissue 4. After the desired quantity of therapeutic substance has been delivered to the location, the distal tip 32 is withdrawn from the myocardium 4 by moving the tube 28 distally slightly. The lumen of the tube 34 is in communication with a pressure monitor as was described in connection with the previous embodiment. Pressure sensing is useful in the present embodiment so that the
15 physician can determine when the distal tip 32 of the tube has penetrated the myocardium 4 so that drugs can be delivered through port 34. In use, the pressure monitor indicates a high pressure when the port 32 is open to the ventricle. However, the pressure reading drops appreciably once the distal port 34 has become submerged within tissue indicating to the user that the distal tip is implanted.

20 As shown in FIG. 8, the withdrawn distal tip 32 and distal portion 30 may be adjusted to locate a new tissue site in the myocardium to deliver the therapeutic substance. The amount of deflection of the distal tip, represented by arrow 40 may be adjusted to reach a new location within the myocardium 4 into which a therapeutic substance needs to be delivered. Additionally, the tube 28 may be rotated, as
25 indicated by arrow 46 to provide a circle of points that are accessible by the deflectable tip tube. A possible new position for the distal portion 30 of the tube is shown in phantom in FIG. 8 to exhibit the steering capabilities of the device.

From the foregoing it will be appreciated that the invention provides a drug delivery device and method for delivering therapeutic substances to the myocardium
30 quickly and accurately by accessing the thorax with a syringe tube device.

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Additionally, the present invention provides a device and method for accessing multiple points on the endocardial surface of the myocardium with a single penetration into the heart.

It should be understood, however, that the foregoing description of the
5 invention is intended merely to be illustrative thereof and that other modifications, embodiments and equivalents may be apparent to those skilled in the art without departing from its spirit. Having thus described the invention, what we desire to claim and secure by Letters Patent is:

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CLAIMS

1. A transthoracic drug delivery device comprising:
a pressure sensing tube and a drug delivery tube joined to the pressure
5 sensing tube in a parallel relationship, but staggered so that one tube extends beyond
the other by a known distance.
2. A therapeutic drug delivery device as defined in claim 1 further
comprising:
10 a pressure sensor joined to the pressure sensing tube and a source of a
therapeutic substance joined to the drug delivery tube.
3. A therapeutic drug delivery device as defined in claim 1 wherein the
known distance between the ends of the staggered tubes is less than the thickness of
15 a subject patient's myocardium.
4. A transthoracic drug delivery device as defined in claim 1 wherein the
pressure sensing tube extends beyond the drug delivery tube.
- 20 5. A thoracic drug delivery device as defined in claim 1 further comprising
a plurality of drug delivery tubes.
6. A method of delivering a therapeutic substance to the myocardium
comprising:
25 providing a delivery device comprised of a pressure sensing tube joined
to at least one drug delivery tube maintained in parallel but staggered so that one
extends beyond the other by a known distance that is less than the thickness of the
myocardium;
Transthoracically accessing the heart;
30 inserting the tubes into the heart;

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monitoring the pressure sensed by the tube while moving the device further into the heart;

stopping advancement of the device into the heart when a dramatic pressure increase is noted indicating pressure sensing tube has entered the ventricle
5 and the delivery tube is within the myocardium;

ejecting a quantity of a therapeutic substance from the delivery tube into the myocardium.

7. A steerable syringe comprising:
10 a delivery tube having a sharpened distal tip, a flexible distal portion, a distal tip, a port and a pull wire for deflecting the distal tip.

8. A transthoracic drug delivery device as defined in claim 7 further comprising a stiffening element slidable within the tube to provide support for the
15 flexible distal portion during delivery of the tube into the heart.

9. A method of delivering a therapeutic substance to a plurality of sites in the myocardium with a single penetration into the heart comprising:
introducing a tube having a deflectable distal portion and distal tip into
20 the left ventricle of the heart;
deflecting the distal tip of the tube so that the tip faces the endocardium;
moving the tube in a proximal direction so that the distal tip penetrates the endocardium;
ejecting a therapeutic substance through the tube into the myocardium;
25 moving the distal tip from the myocardium by advancing the tube distally;
adjusting the position of the tip by changing the deflection angle of the tip or by rotating the tube to a new myocardial location;
moving the tube in a proximal direction to insert the distal tip into the
30 myocardium at the new location;

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ejecting a therapeutic substance from the tube into the myocardium.

10. A method of delivering a therapeutic substance to a plurality of locations within a myocardium as defined in claim 9 wherein the tube is equipped with a
5 pressure sensor and the presence of the distal tip within myocardial tissue is determined by the change in pressure between the pressure indicated when the distal tip is in the myocardium versus the pressure indicated when the distal tip was in the ventricle.
- 10 11. A transthoracic drug delivery device comprising:
a pressure sensing tube and a drug delivery tube joined to the pressure sensing tube.

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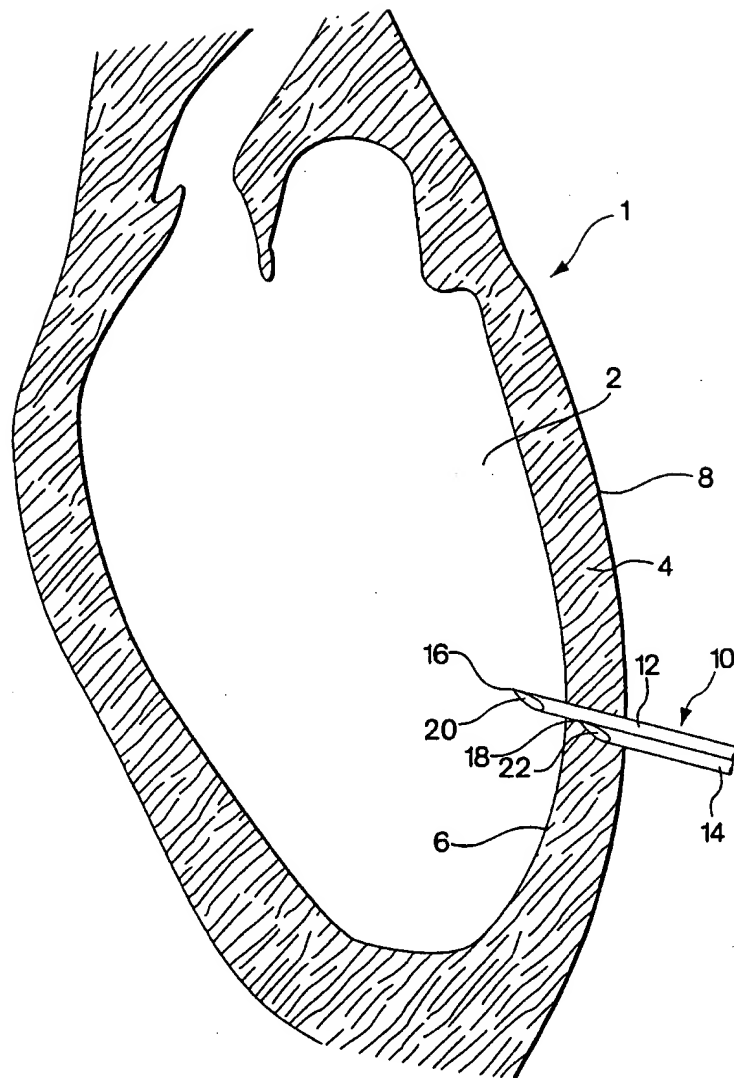


Fig. 1

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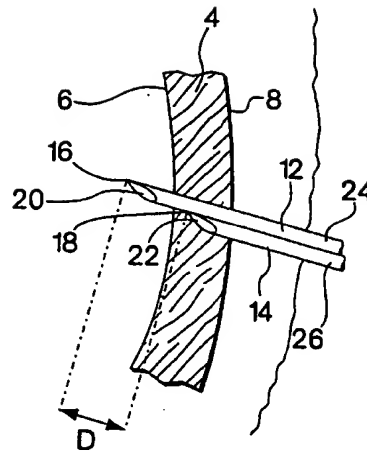


Fig. 2

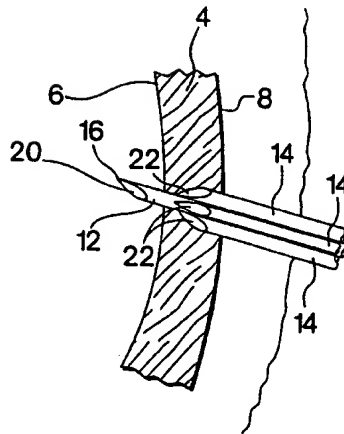


Fig. 3

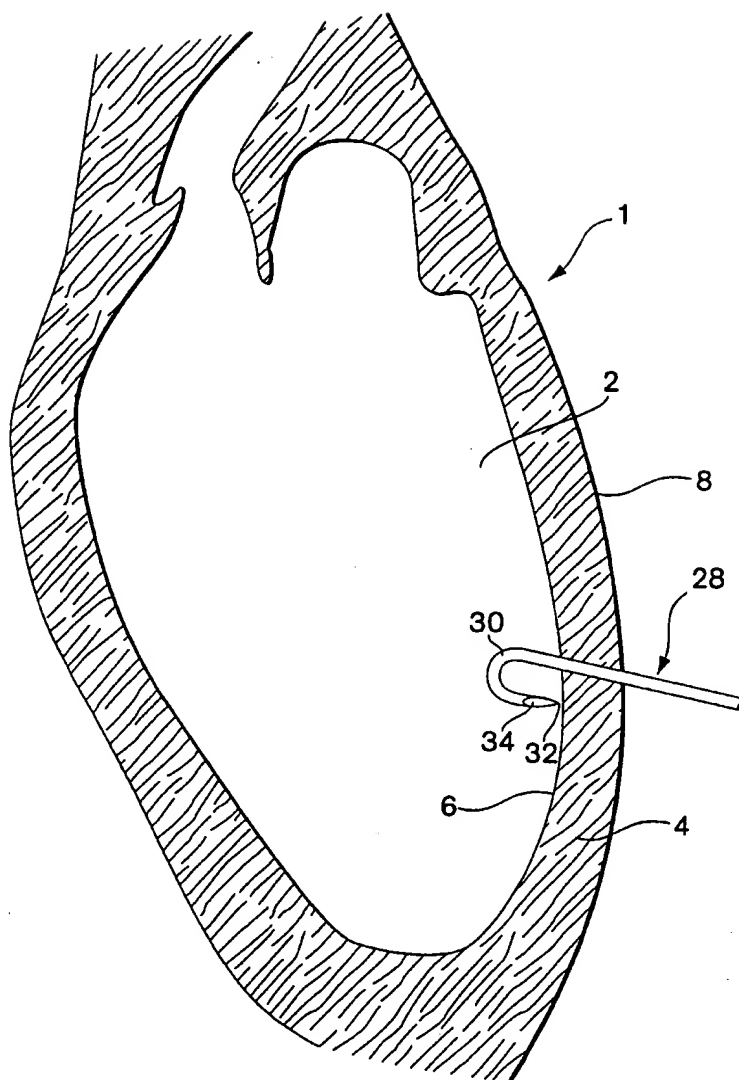


Fig. 4

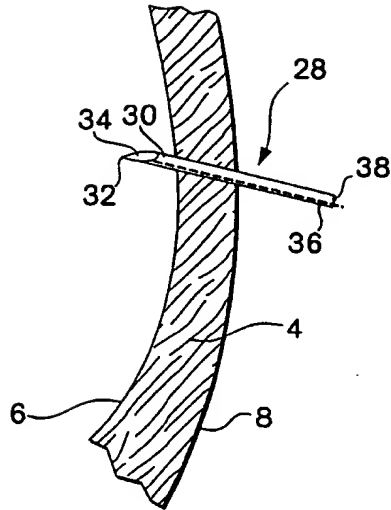


Fig. 5

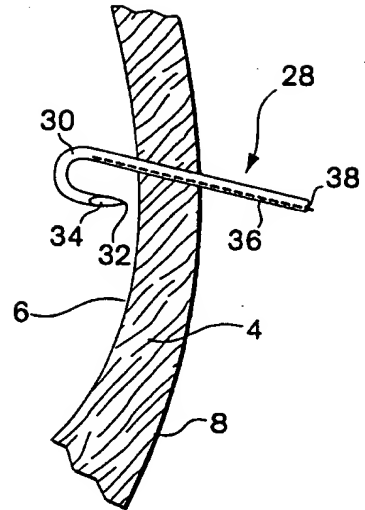


Fig. 6

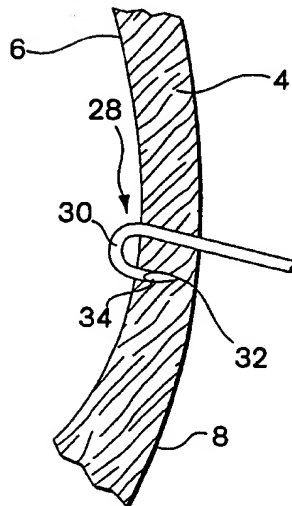


Fig. 7

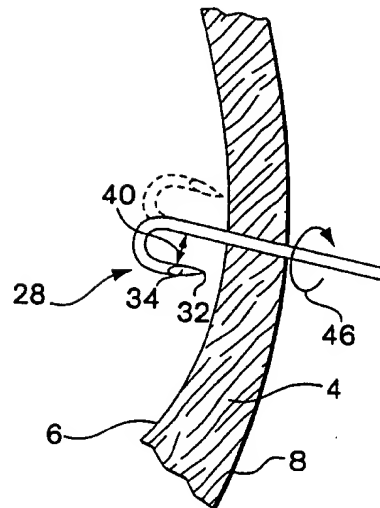
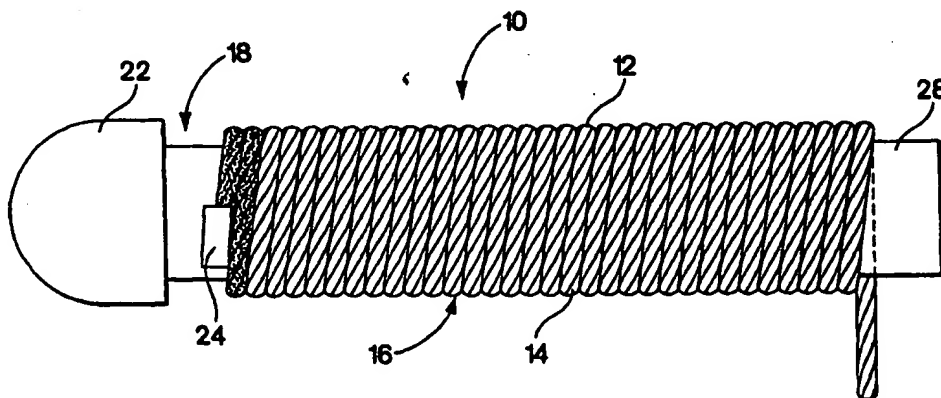


Fig. 8

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(21) International Application Number: PCT/US99/22640 (22) International Filing Date: 29 September 1999 (29.09.99) (30) Priority Data: 09/162,547 29 September 1998 (29.09.98) US (71) Applicant: C. R. BARD, INC. [US/US]; 730 Central Avenue, Murray Hill, NJ 07974 (US). (72) Inventor: GAMBALE, Richard, A.; 382 Dunstable Road, Tyngsboro, MA 01879 (US). (74) Agent: PERULLO, John, F.; Kirkpatrick & Lockhart LLP, 75 State Street, Boston, MA 02109-1808 (US).		(81) Designated States: CA, JP, MX, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>Without international search report and to be republished upon receipt of that report.</i>

(54) Title: DRUG DELIVERY SYSTEMS**(57) Abstract**

The invention includes methods and devices for delivery of one or more therapeutic or diagnostic agents to a body region, such as a blood vessel wall. More specifically, the invention pertains to a drug delivery device that includes a body having a plurality of coils and an interstice that occurs between the coils and wherein a therapeutic or diagnostic agent is carried within the interstice to be delivered to a biological tissue including muscle tissue, neoplastic tissue, vascular tissue, or any other type of body tissue.

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DRUG DELIVERY SYSTEMS

Field of the Invention

The invention relates to systems and methods for the localized delivery of drugs, and
5 in particular, to system and methods for treating arterial and vascular disease, and in particular
for treating coronary conditions and cardiovascular disease.

Background of the Invention

Numerous medical conditions exist in which it is desirable to treat a localized area of
10 disease in a body tissue. Pharmacological interventions aimed at the area of local disease can
be administered systemically or directly. Medication that is administered systemically is
generally distributed through the vascular system, gaining access thereto either by intravenous
or intra-arterial infusion, by intramuscular or subcutaneous injection, or by gastrointestinal
absorption. However, systemic administrations of drugs have systemic effects: drugs
15 administered systemically affect all body tissues. To have an adequate effect on a localized
area of pathology, the drug may need to be administered at levels that are damaging to other
tissues. Untoward side-effects or actual toxicity can result from systemic exposure to certain
drugs, despite favorable local efficacy. Correlatively, a safe level of systemic exposure may
not provide enough local concentration of the pharmacological agent to treat the localized
20 condition. In addition, blood levels of drugs may vary during the process of systemic drug
transport, making total dosage delivered to the diseased area variable. Direct delivery of a
medication to an internal treatment area would minimize systemic effect while maximizing
therapeutic benefit. A locally effective means of administering a pharmaceutical agent could
permit high doses to the diseased tissue while avoiding the side effects or toxicity of systemic
25 exposure.

The treatment of malignant tumors provides an example of a medical condition where
direct delivery would be desirable. Most chemotherapeutic agents for treating malignancies
are administered systemically, through intravenous or intra-arterial infusion. Although the
drugs are intended to affect the neoplasm preferentially, nonetheless they circulate in the
30 bloodstream and have effects on many of the tissues they thereby encounter. These systemic

effects limit the dosage of the drug that can be safely administered and thus limit the drug's overall antineoplastic effect. Delivery systems have been designed to restrict the systemic diffusion of the chemotherapeutic agent, but there remains a need in the art for an apparatus that will permit local and high-dose administration of these powerful medications.

5 Similarly, intravascular pathology is commonly found in discrete areas within blood vessels. These lesions are treated interventionally through balloon dilatation of a region of the artery that has been narrowed by atherosclerosis, a technique known as balloon angioplasty that is well-described in the prior art. However, when this technique is applied to the coronary arteries, in a procedure known as percutaneous transluminal coronary angioplasty (PTCA), the
10 treated vessel loses its patency about 30% of the time. In fact, this re-occlusion, known as restenosis, takes place following any sort of coronary arterial intervention, whether balloon angioplasty, atherectomy, stent placement or laser balloon angioplasty, with restenosis rates of approximately 30% at six months (Kuntz et al., " Novel approach to the analysis of restenosis after the use of three new coronary devices," *J. Am. Coll. Cardiol.* 19:1493, 1992). Vascular
15 injury associated with these interventions is understood to initiate a complex cascade of biologic events, such as thrombosis, vascular smooth muscle cell migration and proliferation and production of extracellular matrix (see e.g., Ip, et al., *J. Am. Coll. Cardiol.* (1990) 1 : 1667-87; Cassells, W., *Circulation* (1992) 86 : 723-9; Schwartz et al., *J. Am. Coll. Cardiol.* (1992) 20 : 1284-93). Data from experimental and clinical studies have suggested that smooth
20 muscle cell proliferation, in particular, represents a key event that ultimately leads to restenosis in up to 50% of all patients within the first 6 months after the intervention (see, e.g., Hanke et al, *Circ. Res.* (1990) 67 : 651-9; Pickering et al. *J. Clin. Invest.* (1993) 91 : 1469-80). When restenosis occurs, further coronary difficulties can be experienced, including arrhythmia, infarcts and even death.

25 The systemic administration of antithrombotic and antiproliferative agents in clinical studies, however, has thus far failed to achieve a significant reduction in the incidence of restenosis (Schwartz et al., supra). One explanation for the failure of such trials is that submaximal doses of standard pharmacologic agents have been used because of concerns that serious side effects might result from systemic administration of the required doses. The
30 concept of local, site-specific delivery of pharmacologic and biologic therapies has evolved as

a solution (see, e.g., March et al., *Cardio Intervention* (1992) 2:11-26). This concept presumes that higher concentrations of a therapeutic agent maybe achieved directly at the angioplasty site, thus avoiding the toxicity associated with systemic levels of the therapeutic agent.

5 The inhibition of smooth muscle cell proliferation has been the primary target for local intravascular drug delivery so far. However, the local delivery approach is likely to prove useful for treating a variety of other cardiovascular conditions as well. This includes local delivery of antithrombotic agents, antibiotics, genes, vectors and other biological agents designed to treat or prevent thrombosis, local deposition of angiogenic growth factors
10 designed to promote neovascularization of an ischemic focus and local administration of agents designed to selectively alter vasomotor tone.

 Approaches for local, intravascular, site-specific delivery of therapeutic agents have included direct deposition of such agents into the vessel wall through an intravascular delivery system. These intravascular delivery systems generally employ balloon catheters which are
15 easily guided through blood vessels to a region in need of treatment and can then be inflated to contact and dilate the entire surrounding vessel wall. A therapeutic agent can then be delivered to the surrounding vessel wall, for example by diffusion through the balloon or by hydrostatic pressure, as occurs when using a porous balloon catheter. However, clinical use of such catheters is limited by certain practical problems, such as leakage of the solution through
20 side branches of vessels and relatively long latency times of 15 to 30 minutes. Furthermore, the inflation pressure required to accomplish a satisfactory seal between the balloon and the surrounding vessel wall can lead to additional vessel injury proximal and distal to the target site, potentially increasing the proliferative response or creating a nidus for thrombus formation.

25 Other balloon catheters which have been used for drug delivery to blood vessel walls are drug-coated catheters (e.g., hydrogel catheters). Upon inflation of the balloon in a blood vessel, the therapeutic agent is "pressed" onto or into the surrounding vessel wall. However, a significant disadvantage of this system is that drugs are rapidly washed off the balloon by exposure to the blood-stream during the catheter's passage to the site (see, e.g., Sheriff et al., *J. Am. Coll. Cardiol.* (1993) 21 : 188A). Typically, the balloon must be chaperoned by a
30

protective sheath as the catheter is advanced toward the target vessel. Similarly, the time between sheath removal and balloon inflation must be minimized to avoid premature shedding of the drug into the blood stream at the site prior to balloon inflation.

As an alternative to drug delivery catheters, stents made of polymeric materials have been used for sustained local drug delivery of antithrombotic or antiproliferative drugs, genes or the like. Several approaches have been investigated to achieve continuous drug release from a stent including, for example, seeding the stent with genetically modified endothelial cells to elute agents such as tissue plasminogen activator and coating the stent directly with drugs or with drug-eluting biodegradable polymers. Although these systems can work well, several drawbacks exist. For example, it can be difficult and cumbersome to expand a stent made of polymeric material, and often such stents are costly to manufacture. Additionally, coated metallic stents can be poorly suited for carrying the necessary quantity of therapeutic agent required for effective treatment.

A need exists for improved methods and devices for local, intravascular delivery of therapeutic agents. A system which delivers a controlled amount of an agent to a blood vessel wall, without creating additional tissue damage or significant inflammatory responses, would satisfy a great need in the art.

Summary of the Invention

Accordingly, it is an object of the invention to provide drug delivery devices that provide for local delivery of an agent in a cost-effective, reliable manner.

It is a further object of the invention to provide a local drug delivery system that can carry selected dosages of agent to the site of treatment.

Other objects of the invention will, in part, be obvious, and, in part, be shown from the following description of the systems and methods shown herein.

Methods and devices are disclosed for delivery of one or more therapeutic or diagnostic agents to a body region, such as a blood vessel or a tissue wall. More specifically, the systems disclosed herein include drug delivery devices that comprise a body having a plurality of coils and interstices that occur between the coils and in which a therapeutic or diagnostic agent can be carried.

The drug delivery devices described herein can be guided into a position adjacent to the region to be treated, using conventional techniques. After positioning the device adjacent to the region to be treated, the device can be expanded so that its drug-containing surfaces come into contact with the surrounding tissue. The agent can then pass from the interstices
5 into the surrounding tissue or interstitial fluid.

In one embodiment, the invention provides devices for delivering an agent to a tissue wall of a body lumen. The devices can include a helical body capable of being biased to unwind from a smaller diameter to a larger diameter, and having an exterior surface with the agent disposed thereon. In a wound condition, the device can be sufficiently small to be
10 delivered transvascularily. By unwinding the helical body from the smaller diameter to a larger diameter, the exterior surface of the helical body can be brought into contact with the tissue of the body lumen for delivering the agent thereto. The helical body can be formed of a spring, such as a spring made of inter-woven filaments. Alternatively, the helical body can comprise a spring that has been formed into a plurality of coils to provide the helical body.
15 For example, in one embodiment, the helical body is formed from an elongate, close-pitched spring watch can be looped into a plurality of coils to provide the helical body of the device. In alternate embodiments, the body comprises a tubular body formed into a plurality of coils. The tubular body can have an interior channel with an outer wall with pores disposed therein for allowing delivery of the agent through the outer wall. Alternatively, the outer wall can
20 include a porous membrane that allows for the delivery of the agent through the outer wall. The tubular body can include a coiled wire disposed within the interior channel for biasing the body to unwind from a first diameter to a second, larger diameter. Alternatively, the interior channel can be adapted to receive a pressurized fluid that can cause the body to unwind from a first diameter to a second diameter. In a further embodiment, the helical body can be formed
25 by a plurality of helical bodies that have been brought together to increase the rigidity of the device, and to increase the radial force developed by the device for more securely holding the device body within the body lumen. In other embodiments, an osmotic gradient within an interior lumen of the helical body can attract tissue fluid into the lumen and cause swelling which can unwind the helical body to bring an agent bearing surface into contact with the
30 tissue wall of the body lumen.

In an alternate embodiment, the device can include a section for engaging with a delivery system. This section can act as a tie down for holding the helical body in a wound condition with a diameter sufficiently small to allow for a transvascular delivery to the site to be treated. Additionally, the device can include an optional recapture element, such as an arm or tail, disposed at one end of the device, that allows a catheter to grip a device deployed within a body lumen for the purpose of retracting the device into a catheter, thereby removing the device from the patient.

In another aspect the device can be understood as a device for delivering an agent to biological tissue which comprises a body having a plurality of coils that are optionally capable of unwinding from a smaller diameter to a larger diameter, and that define a plurality of interstices between the coils, wherein the agent is carried within the interstices to be delivered to the biological tissue of the body lumen upon expansion of the body. The tissue can include muscle tissue, including myocardial tissue, oncological tissue, such as tumor mass, and any other suitable physiological and pathological tissue that can be treated by locally delivered agents. The device can be implanted into the tissue to allow the agent to contact the tissue and allow the agent to reach the tissue being treated, which can be the tissue in contact with the device, tissue adjacent to the tissue in contact with the device, tissue that is brought in contact with the agent by delivery of the agent through the blood stream, or any other tissue that can be reached by the agent to promote a therapeutic effect. Accordingly, the devices and methods described herein can treat restenosis, control angiogenesis and vascularization, deliver chemotherapy agents, deliver anesthetics, or perform any other procedure where local delivery of an agent provides a benefit to the patient.

In another aspect, the invention provides methods for delivering an agent to a tissue wall of the body lumen. These methods can comprise applying the agent to a surface of a helical body capable of being unwound from a first diameter to a second diameter and having a bias tending to unwind the helical body from the first diameter to the second diameter, disposing the helical body within the body lumen, and unwinding the helical body within the body lumen to allow the agent on the surface of the helical body to contact the tissue wall of the body lumen. In one practice, after the device is delivered in its wound state to the site of treatment, the device can unwind in response to its internal bias, which can partially drive the

device open. Alternatively, the helical body can unwind in response to a fluid being delivered into an interior chamber within the helical body, causing the helical body to open. In one practice, the fluid is delivered under pressure, however, in other embodiments, the pressure build up is in response to a fluid gradient that draws fluid into the interior of the interior chamber.

5 The practice of disposing the helical body within a body lumen can be employed in conjunction with the disposition of a stent within a body lumen. In one practice, the helical body drug delivery device is disposed within the body lumen and in an subsequent action a stent is disposed at the same location and coaxial with the helical body thereby providing stent reinforcement of the lumen, as well as local delivery of a therapeutic agent capable of treating restenosis, or treating another condition.

10 The devices described herein can be manufactured by a process that includes winding an elongate body into a plurality of coaxially aligned coils to form a helical body capable of unwinding from a first diameter to a second diameter and applying to the coils an agent for being carried thereon. In one practice, the elongate body is formed by interweaving a plurality of filaments into a cable. The agent can be carried within the interstices that exist between the filaments. Alternatively, the elongated body can be formed from a close-pitch spring that has been wound into a plurality of coaxially aligned coils. The application of the agent can be achieved by applying a gel material containing the agent to the exterior surface defined by the axially aligned coils of the helical body. Alternatively and optionally, the agent can be delivered into an interior channel that extends through the helical body. In further embodiments, the agent can be carried in a sponge material that fits about the exterior surface of a helical spring body. Optionally, the helical spring body can expand, and in this embodiment, place a force on the sponge that drives the agent from the sponge and into the local tissue.

25 For restenosis inhibition, a variety of agents can be employed to achieve the desired therapeutic effect. One class of agents inhibits the proliferation of smooth muscle cells. Other agents which treat restenosis and other diseases, including agents which prevent platelet aggregation and adhesion, such as antiplatelets and anticoagulants, can be employed with the devices described herein. In addition, receptor blockers, growth factors and other hormones

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may be used to limit the normal repair response. The following are groups of particular drugs which can be used to treat vascular disease, such as atherosclerosis and restenosis:

anticoagulants, including heparin, hirudin, hirulog, and tissue plasminogen activator; anti-inflammatory agents, such as steroids, ibuprofen, aspirin, somatostatin, angiotensin, and anti-inflammatory peptide 2; cytotoxins, including colchicine, dexamethasone, doxorubicin, methotrexate, and psoralen; antibiotics; and enzymes and enzyme inhibitors, including urokinase, 2,4-dinitrophenol, and thiol-protease inhibitor and other agents including fibrinogen.

The drug delivery devices and methods described herein can also be used for local, site-specific gene and antisense therapies. In particular, genes, or vectors containing genes, can be delivered which express proteins involved in modulating biologic processes in a body region, such as cell proliferation or matrix production by autocrine means. For example, genes which over express non-secreted growth inhibitors (e.g., tumor suppressor genes) can be transfected into smooth muscle cells present in blood vessel walls to prevent restenosis or proliferation of the cells. Alternatively, to prevent restenosis, genes encoding proteins which cause the death of smooth muscle cells upon exposure to certain drugs can be delivered to blood vessel walls. In one embodiment, genes encoding thymidine kinase are transfected into vascular smooth muscle cells, rendering the cells vulnerable to gancyclovir. Similarly, factors and agents that promote angiogenesis can be carried by the devices, which can be delivered into the myocardial tissue of the heart. The therapies can be employed to treat ischemic tissue and promote the generation or regeneration of heart tissue.

The devices and methods described herein can also be used to treat blood vessel and arterial blockages. In one embodiment, genes encoding growth factors, such as vascular endothelial growth factor (VEGF), which stimulate new blood vessel growth, are delivered to the walls of blocked vessels to promote the generation of new vessels which bypass the obstruction.

The drug delivery systems provided by the invention also help avoid the problem of overdosage associated with systemic delivery of drugs, by enabling a controlled amount of a selected therapeutic or diagnostic agent to be directly deposited onto a specific region of

tissue. Furthermore, the systems allow for selective delivery of therapeutic or diagnostic agents to vessel walls. The system also solves the problems of drug washoff or leakage.

Overall, the described methods and drug delivery devices provide a safe and effective means for local, site-specific delivery of a wide variety of therapeutic agents to vascular and other body tissues.

Brief Description of the Figures

The foregoing and other objects and advantages of the invention will be appreciated more fully from the following further description thereof, with reference to the accompanying drawings wherein:

Fig. 1 is an illustration of one embodiment of a drug delivery system for insertion into a body lumen;

Fig. 2 provides an end view of the device of Fig. 1;

Fig. 3 depicts in greater detail one cable suitable for forming the drug delivery device of Fig. 1;

Fig. 4 depicts a method of forming the device of Fig. 1;

Fig. 5 depicts an expanded helical body in a body lumen;

Figs. 6A-6B depict an alternative embodiment of a device for local drug delivery;

Fig. 7 depicts one process for forming the device of Fig. 6A;

Figs. 8 and 9 depict an alternative embodiment of a device for local drug delivery having a portion for being gripped by a delivery system;

Figs. 10 and 11 depict an alternative embodiment of a device for local drug delivery; and

Figs. 12 and 13 depict a delivery system for delivering drug delivery devices.

Detailed Description of the Illustrated Embodiments

To provide an overall understanding of the invention, certain illustrative embodiments will now be described, including a drug delivery device having a helical body and an exterior surface with a therapeutic agent carried thereon. However, it will be understood by one of

ordinary skill in the art that the devices and methods described herein can be adapted and modified to provide systems that can support a vessel wall, deliver a drug to muscle tissue, or any other suitable body tissue, or for any other suitable application. Other changes, additions and modifications can be made to the invention without departing from the scope hereof.

5 Fig. 1 depicts a drug delivery device 10 that includes a cable 12 that forms a helical body 16 having an exterior surface that can carry a coating 14 containing an agent to be delivered to a tissue wall of a body lumen.

 In the depicted embodiment, the helical body 16 of the device 10 is formed as a spring having a closed-pitch, such that adjacent coils of the helical body 16 are in contact, or
10 substantially in contact. In alternative embodiments, the helical body can have an open-pitch wherein adjacent points on separate coils are longitudinally spaced from away from each other. Further embodiments of the helical body 16 can include bodies that are combinations of closed-pitch and open-pitch sections.

 As further shown in Fig. 1, the device 10 includes an interstice 19 that is formed as a
15 helical groove on the exterior surface of the body 16 and that extends along the full length of the body 16. The depicted interstice 19 arises from the space that is formed between abutting coils of the helical body 16 and the interstice 19 extends partially into the exterior surface of the helical body 16. In other embodiments, wherein the adjacent coils are non-contiguous, the interstice 19 can extend through the exterior surface of the helical body 16. The interstice 19
20 provides a space for receiving and carrying an agent, such as a therapeutic agent for treating restenosis. The interstices 19 can increase the amount of coating 14 that can be carried by the exterior surface of the drug delivery device 10 by increasing the surface area of the device 10 relative to a device that has no interstices and by coating spaces in which a coating can reside.

 Fig. 2 provides a cross-sectional view of the device 10. Specifically, Fig. 2 shows that
25 the helical body 16 of the device 10 defines an interior lumen 17 that extends longitudinally through the body 16 for the full length of the body 16. As the device 10 can be disposed within a body lumen, such as a coronary artery, it will be understood that the lumen 17 allows for fluid flow through the device 10. Fig. 2, further illustrates that the interior surface of the device 10 is substantially smooth, lacking any elements that extend into the lumen 17. This
30 smooth interior surface is understood to reduce the likelihood of thrombus formation and

subsequent flow obstruction. Fig. 2 further illustrates the diameter of the helical body 16. The diameter of the helical body 16 is variable, as the helical body 16 can be coiled, in a spring-like manner, about a longitudinal axis that extends through the helical body 16. This variable diameter facilitates transvascular delivery, as the diameter of the device 10 can be sufficiently reduced to allow the delivery device 10 to fit within and pass through the lumen of an artery or vein of the patient being treated. Accordingly, it will be understood that the delivery device 10 can have a wound state and an unwound state, wherein the delivery device in the wound state has a diameter that is sufficiently small to allow for transvascular delivery and the diameter of the delivery device 10 in the unwound state can be sufficiently large to allow the exterior surface of the helical body 16 to contact the tissue wall of the body lumen in which the device 10 is disposed.

The depicted delivery device 10 is dimensionally adapted for being transvascularly delivered. Specifically, the depicted embodiment is approximately 3 mm in diameter and about 3 cm long. However, the device can be sized for the patient and application, and the diameter can range for example from between 1 mm to about 5 mm, and the length can also vary depending on the application, from .25 cm to about 7 cm. When wound down to a reduced diameter, the device 10 can have a diameter of approximately about .5mm, and when implanted in a body vessel, the device 10 would unwind to a diameter sufficiently large to engage the sidewall of the body vessel. Additionally, the device 10 can unwind to contact the tissue wall with sufficient radial force to secure the device 10 within the vessel and resist downstream movement caused by fluid pressure generated from blood flow.

To facilitate expansion of the delivery device 10 from a first diameter to a second larger diameter, the helical body 16 has a bias that tends to resist being placed in the wound state. To this end, the coils of the depicted helical body 16 are sufficiently resilient to tend to resist rotation or winding, such that rotating the coils around the longitudinal axis places the helical body 16 under tension. This force provides a bias that tends to unwind the helical body 16 and expand the diameter of the device 10 to achieve the diameter of the unwound state. To achieve this resiliency, the helical body 16 can be formed from a material having sufficient elasticity to resist plastic deformation as the body 16 is wound to a reduced diameter. The depicted helical body 16, is formed of a cable 12 made of a plurality of interwoven filaments

of elastically deformable material, such as stainless steel 316. The cable 12 can be formed into a plurality of coils to provide the helical body 16. In alternative embodiments, the cable 12 can be formed of other bio-compatible materials, including polymeric materials. Additionally, the device 10 can be formed of bio-absorbable material, thereby allowing the device 10 to be absorbed over time within the body lumen.

Fig. 3 depicts the individual filaments that are interwoven or intertwined, to form the cable 12 depicted in Fig. 1. As shown by Fig. 3 a plurality of individual filaments 20 are intertwined together to form a cable that is substantially straight and flexible. Each of the depicted filaments 20 can be a strand of a bio-compatible material, such as a metallic or polymeric material, that can be interwoven to form the depicted cable. In one embodiment, the strands 20 are of different materials, including materials containing therapeutic agents for purposes of delivering a drug or a plurality of drugs to the tissue wall of the body lumen, as well as materials selected to achieve a desired flexibility, resiliency, or hoop-strength. It will be apparent to one of ordinary skill in the art that the filaments 20 can be selected to achieve a variety of desired characteristics for the cable 12, and variations in the selection of materials, the methods for interweaving, the additions of adhesives, photo-active compounds or other materials are modifications understood to be within the scope of the invention.

Fig. 4 depicts one process for forming the drug delivery device 10. Specifically, Fig. 4 depicts a mandrel 18 about which the cable 12 is wound. The mandrel 18 includes a handle 22, a chuck 24 and a shaft 28. As shown in Fig. 4, one end of the cable 12 is attached to and held stationary by the chuck 24. The cable 12 can be wound about the shaft 28 of the mandrel 18 causing the cable 12 to coil around the shaft 28 and form into a helical body. The other end of the cable 12 extends freely from the mandrel and can be cut after a selected number of turns are formed on the mandrel to provide a helical body 16 of selected size. The materials selected for forming the cable 12 can impart to the cable 12 a sufficient amount of plastic deformation to allow the cable 12 to be wound on a mandrel, such as the mandrel 28 depicted in Fig. 4, to achieve and to maintain a helical shape. Optionally, the material of the cable 12 can be heated during the process of forming the coils, to facilitate formation of the device 10. In other practices, wherein other materials are employed, such as polymeric materials, treating reagents such as resins, can be applied to the coils to achieve the desired rigidity and

resiliency. Once the cable 12 is cut, the chuck 24 can be released so that the wound cable 12 can be slidably removed from the mandrel 18. The drug delivery device 10 can then be placed on an intravascular delivery system that can carry the drug delivery device 10 to the site of deployment within the patient. Although Fig. 4 depicts one process for forming the body of one device according to the invention, it will be understood that other processes can be employed, including processes that involve injection molding, casting processes, laser cutting or etching processes, without departing from the scope of the invention.

Once the body is formed, the coating 14 can be applied to the exterior surface of the device 10, wherein the coating includes at least one agent to be delivered to the vessel wall. The coating 14 can include anti-thrombotic and anti-proliferative agents suitable for reducing the likelihood of restenosis occurring in the vessel. The coating can be applied by dipping the device into a liquid material that will dry to form a coating on the device. In this practice the coating can be formed over the entire exterior and interior of the device, or over a portion of the exterior and interior surfaces. In other processes the coating is formed by brushing a material onto the exterior surface of the device. Other techniques can be employed for coating the device, and the subject matter of the invention is not to be limited to any particular technique or practice. The coating can be placed over the entire exterior of the device, or over selected regions, such as within the groove 19. Additionally, the coating can have alternate thicknesses along the length of the surface and the thickness of the coating can be employed, among other techniques, for controlling the amount of agent delivered to the tissue. The coating can include drug-impregnated gels or polymers capable of being deposited at the endoluminal wall. For the embodiment depicted in Fig. 1, the gel can coat the cable 12, allowing material to travel into the interstices between the coils of the helical body 16 and between the filaments 20 of the cable 12. The agent carried by the coating can be any agent suitable for treating one or more of the conditions that can effect the vascular system, or tissue proximate the vascular system. These agents can include agents for treating restenosis, coronary artery occlusion, myocardial ischemic syndrome, cardiac conduction disturbances or any other condition.

For localized treatment of diseases, the coatings can include agents such as hirudin, argatroban, forskolin, hirulog, heparin, tPA, urokinase, streptokinase, calcium channel

blockers, angiotensin converting enzyme inhibitors, fish oil, and growth peptides, thromboxane synthetase inhibitor, serotonin antagonists, HMGCoA, reductase inhibitors, platelet derived growth factors, inflammatory cell factors, platelet aggregation inhibitors, and thrombin inhibitors such as hirudin or its analogs, vapiprost, prostacyclin and prostacyclin analogues, dextran, D-phe-pro-arg-chloromethylketone, dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antibody, recombinant hirudin, thrombin inhibitor, angiopeptin, angiotensin converting enzyme inhibitors, (such as Captopril, available from Squibb; Cilazapril, available for Hoffman-La Roche; or Lisinopril, available from Merck), colchicine, fibroblast growth factor antagonists, fish oil, omega 3-fatty acid, histamine antagonists, HMG-CoA reductase inhibitor, methotrexate, monoclonal antibodies, nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitor, seramin, serotonin blockers, steroids, TRANIRAST, thioprotease inhibitors, triazolopyrimidine and other PDGF antagonists, alpha-interferon and genetically engineered epithelial cells, and combinations thereof. The coating material can be bioabsorbable. While the foregoing therapeutic agents have been used to prevent or treat restenosis and thrombosis, they are provided by way of example and are not meant to be limiting, as other therapeutic drugs may be developed which are equally applicable for use with the invention.

Fig. 5 depicts one drug delivery device 30 deployed within a vessel of a patient, such as within a coronary artery. As shown in Fig. 5, the drug delivery device 30 has unwound to an increased diameter that is sufficiently large to engage against the tissue wall of the body lumen. Accordingly, the exterior surface of the drug delivery device 12 is in contact with the tissue wall, thereby contacting the tissue wall with the agent carried in the exterior surface of the drug delivery device 30. In this way, a therapeutic, diagnostic or other type of agent carried on the exterior surface of the delivery device 30 can contact, and be absorbed by, the tissue to be treated. Additionally, the bias of the device 30 provides a force projecting radially outward that tends to secure the device 30 within the body vessel.

Figs. 6A and 6B depict an alternative embodiment of an implantable device for local drug delivery. Specifically, Fig. 6A depicts a delivery device 40 that includes a helical body 46 formed as a wound spring of bio-compatible material with an exterior surface 44 that can carry the agent to be delivered to the site of treatment. Accordingly, the device 40 can be

understood as a compound spring in that it includes a helical, spring-like body 46 that is formed from a smaller spring 42 that has been wound into a plurality of coils. The compound spring structure of the drug delivery device 40 is also shown by Fig. 7 that illustrates in more detail one process for forming the helical body 46 of the device 40. Specifically, Fig. 7 illustrates the spring 42 being wound on a mandrel 50 that mounts to a handle 52 and includes a chuck 54. As shown, the spring 42 can be wound into a plurality of coils that form the helical body 46 of the device 40 in a process that is similar to the process described with reference to Fig. 4. The spring 42 can be formed of a bio-compatible material and generally can be understood as a spring formed of a material that is sufficiently plastically deformable to allow the spring 42 to be wound on the mandrel 50 and shaped into the helical body 46 depicted in Fig. 6. As discussed above, the winding process illustrated by Fig. 7 can be accompanied by a heating process or chemical treatment process that allows the spring 42 to take on and maintain the shape of the helical body 46.

Returning to Fig. 6A it can be seen that the exterior surface 44 of the helical body 46 includes an interstice 48 that curves around the exterior surface 44 and that extends along the full length of the body 46. As discussed above with reference to the embodiment of Fig. 1, the interstice provides a space for receiving a coating that can carry the agent to be delivered to the tissue wall. Fig. 6B illustrates in greater detail and in cross-section one portion of the spring 42. Specifically, Fig. 6b depicts that the spring 42 is formed from a coiled spring wherein adjacent coils of the spring 42 form the depicted interstices 49 that are also capable of carrying an agent to the tissue in which the device is implantable. Fig. 6B further depicts that the spring 42 includes a lumen 47, which optionally can carry an agent to the tissue. This agent can be the agent applied as a coating to the exterior surface 44 of the device 40, or can be a different material, or a combination of both materials.

Figs. 8 and 9 depict a drug delivery device 60 that includes a tie down 62 located at the midpoint of the delivery device 60. As shown in Fig. 8, the tie down 62 is formed from a U-shaped bend that is disposed within the helical body of the device 60. The helical body of the device 60 is formed from a coiled spring, similar to the device depicted in Fig. 6. The tie down 62 provides a handle that can be engaged and held by a transvascular delivery system to hold the drug delivery device 60 in a wound condition. Upon release of the U-shaped handle, the

drug delivery device will begin unwinding at its central location. This is understood to reduce the likelihood that trauma to the blood vessel will occur by lashing that can arise from the unwinding of the ends of the helical drug delivery device 60. Fig. 9 depicts the cross-section of the device 60, which is similar to that depicted in Fig. 2. It will be understood that although
5 the depicted spring is a compound spring device, such as those shown in Fig. 6A, in other embodiments, the spring can be formed from a cable such as the devices depicted in Fig. 1, or any other suitable device.

Figs. 10 and 11 depict a further alternative embodiment of a drug delivery device suitable for delivering an agent to a tissue wall of a body lumen. Specifically, Fig. 10 depicts
10 a drug delivery device 70 formed from a cylindrical tube 72 that has been wound into a helical body 74. The helical body 74 can be formed of a tubular rod of bio-compatible material, such as stainless steel 316, and the process employed for forming the tubular rod into the helical body 74 can be similar to the methods described with reference to Fig. 4. The helical body 74 can include a groove 76 that is formed by the space between the adjacent coils of the helical
15 body 74. The exterior surface of the device 70 can be coated with an agent to be delivered to the tissue wall of the body lumen. Any suitable agent can be carried on the exterior surface.

In the depicted embodiment, the cylindrical tube 72 from which the helical body 74 is formed has an interior lumen. Accordingly, the interior lumen provides an interior channel through the coils of the helical body 74. In one embodiment, one end 78 of the helical body is
20 sealed to form a lumen, closed at one end, and thereby adapted for receiving fluid at one end and maintaining fluid therein. Accordingly, a pressurized fluid can be delivered into the interior lumen of the helical body 74. It is understood that delivery of the pressurized fluid into the interior channel of the helical body 74 causes the helix to unwind, thereby expanding the radius of the drug delivery device 70. In one embodiment, the helical body 74 is formed
25 of a porous material that allows the fluid delivered into the interior chamber to pass to the exterior of the device and contact the tissue in which the device is implanted. In this embodiment, the porosity of the wall can be sufficiently limited to prevent rapid release of the delivered fluid and therefore allow sufficient pressure to build within the interior chamber to cause the helical body 74 to unwind. The unwinding of the helical body 74 can be

accompanied by a plastic deformation of the device, such that the device can maintain its unwound condition, therefore remaining securely within the body lumen.

In an alternative embodiment, the interior channel of the tubular body carries a resilient wire element that biases the tubular body 74 to tend to unwind the helix of the body 74 to increase the diameter of the drug delivery device 70, thereby allowing contact of the exterior surface of the drug delivery device 70 with the tissue wall of the body lumen being treated. For example, the tubular body can be formed of a polymeric material, or a graft type material, and a resilient coil, such as a coil formed of stainless steel, can be threaded through the interior lumen of the tubular body. The resilient coil provides the tubular body with a bias that tends to unwind the body and expand the body from a smaller diameter to a larger diameter. In this way the internal wire tends to drive the surface of the body into contact with the tissue in which the device is implanted. Optionally, an expandable material can be placed into the interior of the tubular body. The expandable material can contact a body fluid, such as blood, or can respond to the body heat of the patient, to drive the body open and contact the body against the tissue.

The deployment of the drug delivery systems described above can be accomplished by any suitable system, including those described in U.S. Patent 5,372,600, the teachings of which are herein incorporated by reference. One illustrative system is depicted in Figs. 12 and 13. Specifically, Fig. 12 depicts a portion of a catheter 90 and a drug delivery device 92 that sits around the periphery of the catheter 90. The catheter 90 can be an elongate tubular body formed of a bio-compatible material and sufficiently long and narrow to allow for transvascular access to the site of treatment. Fig. 12 depicts only the distal portion of the catheter 90, for which in one embodiment the catheter can be 100 to 300 cm in length. The embodiment depicts a drug delivery device 92 that is a compound spring delivery device with an intermediate tie-down, similar to the device depicted in Fig. 8. For the depicted delivery device 92, the ends 94 of the device 92 are terminated in bulbous sections, and the mid-point 96 also has a bulbous section. As illustrated, the bulbous sections are disposed within a plurality of apertures 100, 102 and 104 located on the periphery of the catheter 90. The apertures provide openings to a lumen 108 that extends through the interior of the catheter 90. The bulbous sections fit within the apertures and act to retain the drug delivery device 92 on

the catheter 90 and in a wound condition. In the depicted embodiment, the bulbous sections fit into the apertures so that the bulbous members catch on the lip formed by the perimeter of the aperture. In this way, the end and mid-sections of the device 92 are prevented from sliding out of the apertures 100, 102, and 104, which act as clasps for securing the device 92 to the
5 body of the catheter 90.

Within the catheter and proximate the lumen 108, two release wires 110 and 112 are disposed within lumens that run along the length of the catheter 90 adjacent to the apertures 100, 102 and 104. The release wires are also shown in Fig. 13. Each of the release wires 110 and 112 has at least one push member 114 that can slide within its respective lumen and pass
10 by one or more of the apertures 100, 102 or 104. The push member 114 can slide past an aperture and push laterally the bulbous section of the drug delivery device away from the lip of the aperture, causing the bulbous member to be released from the aperture. Accordingly, in the depicted embodiment, where the release mechanism includes the separately controllable release wires 110 and 112, the operator can pull the release wires to free the drug delivery
15 device 92 from the catheter 90 and allow the device to unwind and contact the tissue into which the device 92 is being implanted. In one practice, the release wire 110 is operated first to allow the mid-section of the device 92 to be released. This allows the device to begin unwinding at the midpoint and reduces the force at which the end sections will unwind. This is understood to provide a more gentle deployment of the device 92 and to reduce the
20 likelihood of tissue trauma caused by the unwinding ends of the drug delivery device 92. In a second step, the operator can pull on the release wire 112 to cause the pull member 114, or two pull members 114, to slide past the apertures 100 and 104 and release the end sections of the device 92. By releasing the end sections, the drug delivery device 92 can be fully
deployed.

25 Although the embodiment depicted in Figs. 12 and 13 employs a drug delivery device with bulbous terminations at the end points and midpoints, it will be understood that other embodiments can employ other mechanisms for retaining the drug delivery device on the catheter 90. For example, the ends and mid-sections can employ notched exterior surfaces, wherein the notches are adapted to engage with a tab located adjacent the apertures. Upon
30 moving the push member past the aperture, the grooved section is pushed laterally from the

tab, freeing that section of the device. Alternatively, the device 92 can be provided with loops that extend into the apertures and can slidingly receive a release wire, such as the depicted release wires 110 and 112.

Those skilled in the art will know or be able to ascertain using no more than routine experimentation, many equivalents to the embodiments and practices described herein. For example, different materials can be employed for forming the helical body, including composite materials, biodegradable materials, or any other suitable materials. One material can be Nitinol wherein the wound body can expand in response to body temperature of the tissue in which the body is placed. Additionally, the helical body of the device can comprise a plurality of helical bodies, intertwined together. It will also be understood that the systems described herein provide advantages over the prior art including allowing recapture of the drug delivery device, as well as providing a device well suited for use in concert with a stent that supports a weakened or obstructed cardiac artery. Additionally, the drug delivery devices described herein can be employed for delivering drugs to muscle tissue and other types of tissue. Accordingly, it will be understood that the devices described herein can be used in conjunction with delivery systems that can penetrate tissue such as muscle tissue and skin. Similarly, the devices described herein can be employed for delivering agents to the aorta, the iliacs, the urethra, or any internal body lumen.

Accordingly, it will be understood that the invention is not to be limited to the embodiments disclosed herein, but is to be understood from the following claims, which are to be interpreted as broadly as allowed under the law.

- 20 -

1 claim:

1. A device for delivering an agent to a biological tissue, comprising
a helical body capable of being biased to unwind from a first smaller diameter
5 to a second larger diameter, and
having an exterior surface with the agent disposed thereon, whereby unwinding
of said helical body from said first diameter to said second diameter allows said agent to
engage the tissue for delivering the agent thereto.
- 10 2. A device according to claim 1, wherein said helical body comprises a spring.
3. A device according to claim 1, wherein said helical body comprises a spring formed of
a cable made of interwoven filaments.
- 15 4. A device according to claim 3, wherein said interwoven filaments define interstices
capable of carrying the agent to be delivered.
5. A device according to claim 3, wherein said interwoven filaments include a filament
comprising the agent to be delivered.
- 20 6. A device according to claim 1, wherein said helical body comprises a spring formed
into a plurality of coils to provide said helical body,
7. A device according to claim 1, wherein said body comprises a tubular body formed
25 into a plurality of coils.
8. A device according to claim 7, wherein said tubular body includes an interior channel
and a porous outer wall for allowing delivery of the agent through said outer wall.

9. A device according to claim 7, further including a coiled wire disposed within said tubular body to provide the bias to said body to unwind from said first diameter to said second diameter.
- 5 10. A device according to claim 1, wherein the helical body comprises a spring having a sponge covering.
11. A device according to claim 7, further including an interior channel disposed within said tubular body and having pressurized fluid therein for biasing said body to unwind
10 from said first diameter to said second diameter.
12. A device according to claim 7, further including an interior channel disposed within said tubular body and an expandable foam body within said interior channel and being adapted for expanding in response to absorbing a body fluid for biasing said body to
15 unwind from said first diameter to said second diameter.
13. A device according to claim 1, wherein said helical body comprises a plurality of helical bodies.
- 20 14. A device according to claim 1, further including a section for engaging a delivery system.
15. A device for delivering an agent to biological tissue, comprising
a helical body having a plurality of coils and being capable of unwinding from
25 a smaller diameter to a larger diameter, and
a plurality of interstices occurring between said coils, wherein the agent is carried within said interstices to be delivered to the biological tissue upon expansion of the helical body.
- 30 16. A method for delivering an agent to a biological tissue, comprising

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applying the agent to a surface of a helical body capable of being unwound from a first diameter to a second diameter and having a bias tending to unwind said helical body from said first diameter to said second diameter,

disposing said helical body within the biological tissue, and

5 unwinding said helical body within the biological tissue to allow the agent on the surface of the helical body to contact the tissue wall of the body lumen.

17. A method according to claim 16, wherein unwinding said helical body includes allowing the bias to drive open said helical body.
- 10 18. A method according to claim 16, wherein unwinding said helical body includes providing said helical body with an interior channel and delivering a pressurized fluid into said channel for opening said helical body.
- 15 19. A method according to claim 16, further including disposing the helical body within a body lumen, and disposing a stent within the body lumen and coaxial with said helical body.
- 20 20. A method according to claim 16, further including disposing the helical body within a biological tissue comprising muscle tissue.
- 25 21. A method according to claim 16, further including disposing the helical body within a biological tissue comprising a pathological tissue.
- 30 22. A method for manufacturing a device for local delivery of an agent, comprising winding an elongate body into a plurality of coaxially aligned coils to define a helical body having a plurality of mating interstices, and applying the agent to said interstices for allowing the agent to be carried thereon.

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23. A method according to claim 22, further including
forming said elongate body by interweaving a plurality of filaments to form a
cable.
- 5 24. A method according to claim 23, wherein applying the agent to said interstices
includes allowing the agent to be carried within interstices between the interwoven
filaments.
25. A method according to claim 22, further including providing a close-pitch spring as
10 said elongate body.
26. A method according to claim 22, wherein applying an agent includes applying to said
interstices a gel material containing the agent.
- 15 27. A method according to claim 22, including applying the agent to an interior channel
defined by said coaxially aligned coils.
28. Apparatus for delivering an agent, comprising
a plurality of mating surfaces disposed adjacent to each other to form
20 interstices therebetween, and
an agent being disposed within the interstices.
29. Apparatus according to claim 28, wherein
said plurality of mating surfaces are formed from adjacent coils of a helical body.
- 25 30. Apparatus according to claim 28, wherein
said plurality of mating surfaces comprise a cable formed of interwoven
filaments and coiled into a helical body.
- 30 31. Apparatus according to claim 28, wherein

said plurality of mating surfaces comprise a helical body formed of an elongate spring that has been wound into a plurality of coils.

32. Apparatus according to claim 29, wherein

5 said helical body includes a mechanism for cooperating with a delivery system to thereby allow mechanical assisted delivery of the helical body.

33. Apparatus for disposing a drug delivery device within a body lumen, comprising
an elongate tubular body having a distal end adapted for carrying the drug

10 delivery device, and

a central latch disposed proximally of said distal end and adapted for engaging a mid-section of the drug delivery device, whereby said central latch secures the mid-section of the drug delivery device to the elongate tubular body for allowing delivery thereof

15 34. Apparatus according to claim 33, further comprising

a release element extending through said elongate tubular body and coupled to said latch for operating said central latch to release the mid-section of the drug delivery device.

20 35. Apparatus according to claim 33 further comprising,

a distal latch and a proximal latch each disposed adjacent to said central latch and each capable of engaging the drug delivery device at a respective one of the distal or proximal ends of the drug delivery device.

25 36. Apparatus according to claim 33, further comprising

a release mechanism capable of being operated to release said distal, central and proximal latches in a sequence in which said central latch is released prior to said distal and proximal latches.

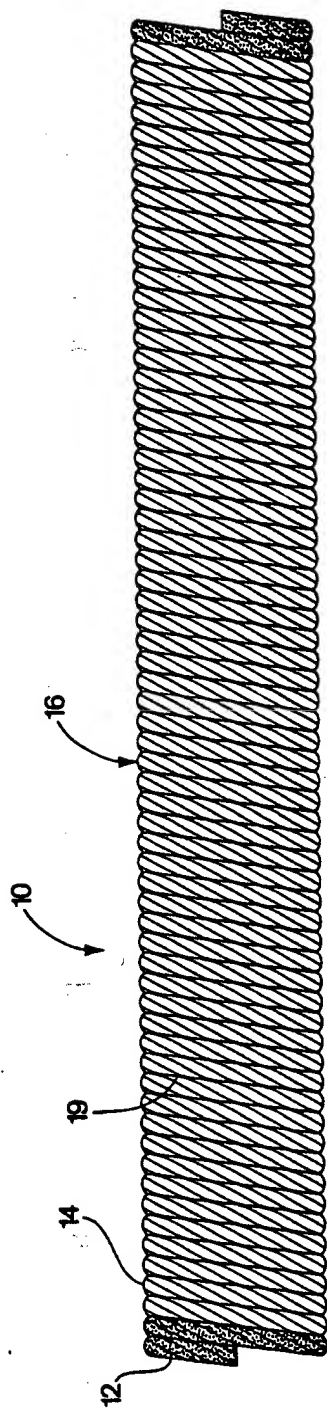


Fig. 1

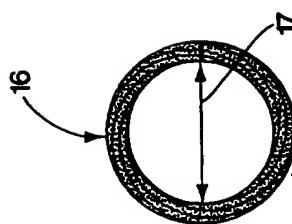


Fig. 2

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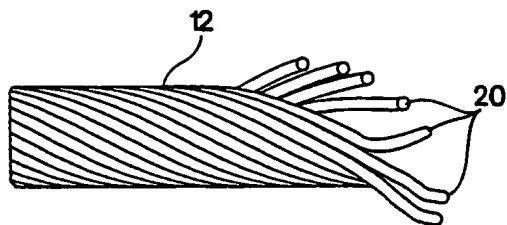


Fig. 3

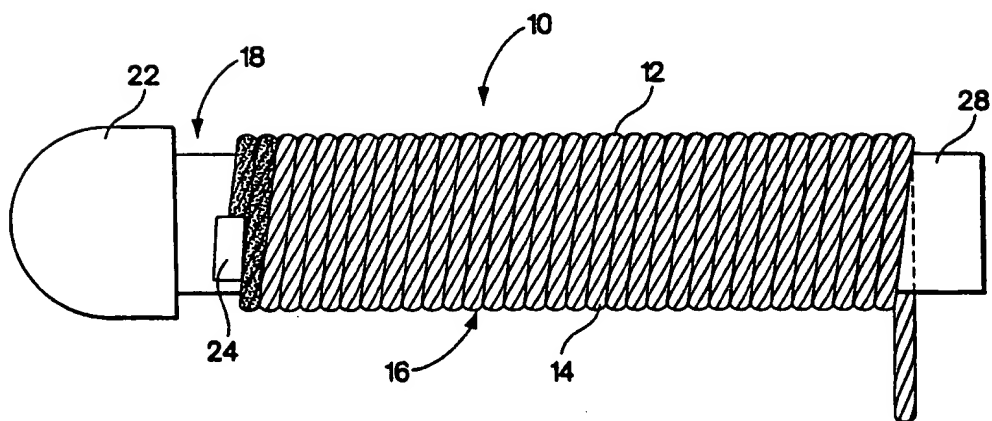


Fig. 4

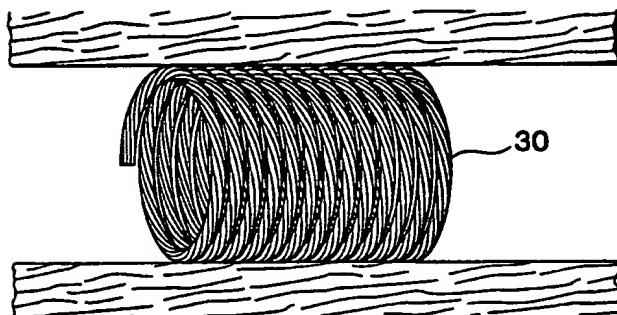


Fig. 5

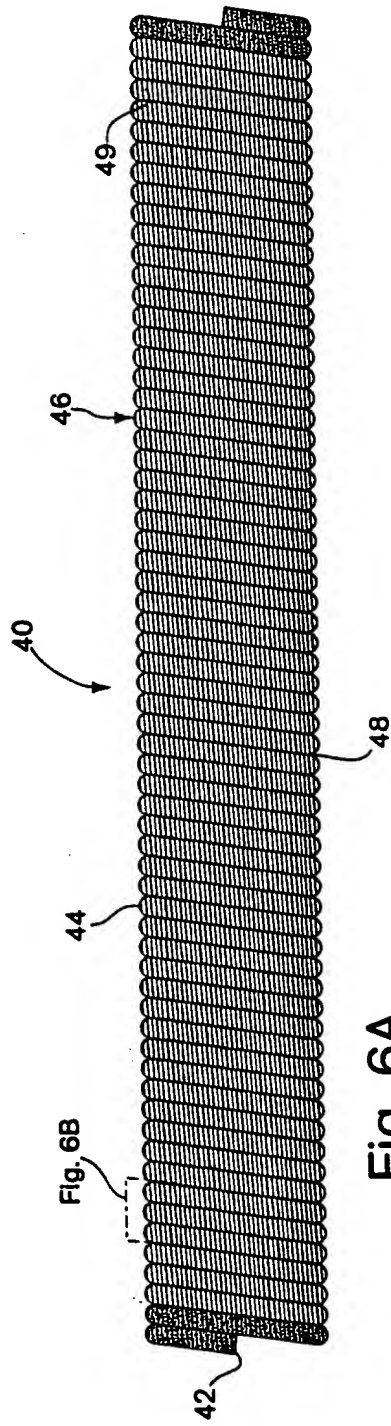


Fig. 6A

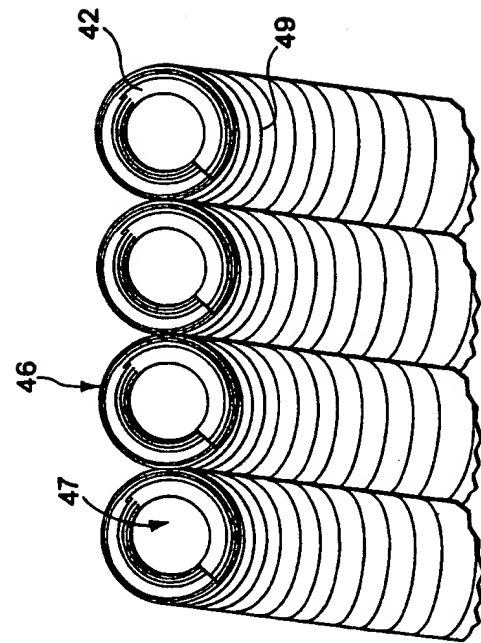


Fig. 6B

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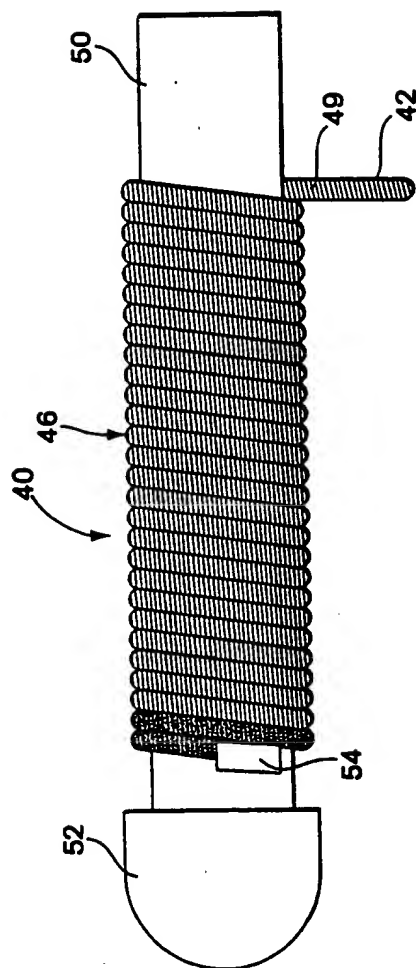


Fig. 7

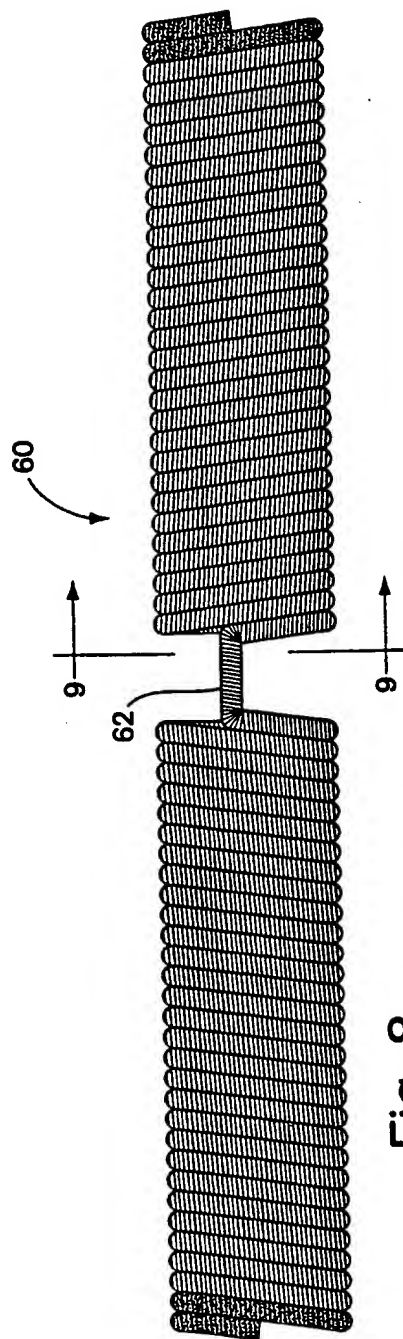


Fig. 8

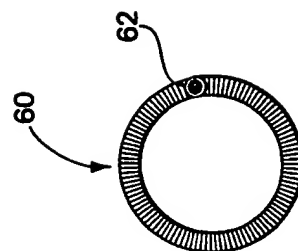


Fig. 9

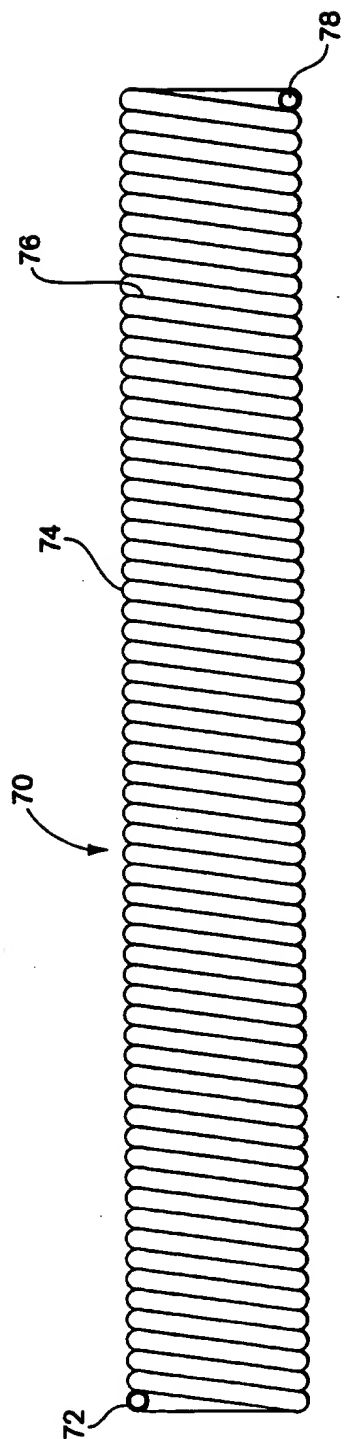


Fig. 10

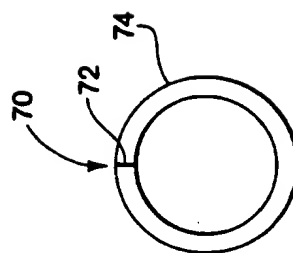


Fig. 11

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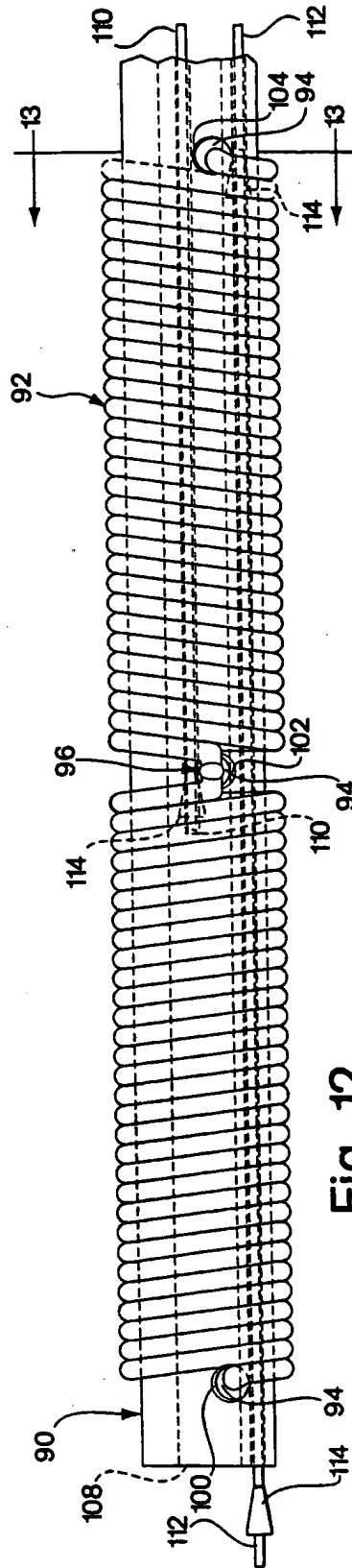


Fig. 12

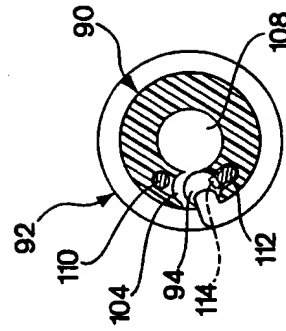


Fig. 13

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